Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 16 SEP 2005 HIGHEST RN 863378-74-9
DICTIONARY FILE UPDATES: 16 SEP 2005 HIGHEST RN 863378-74-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

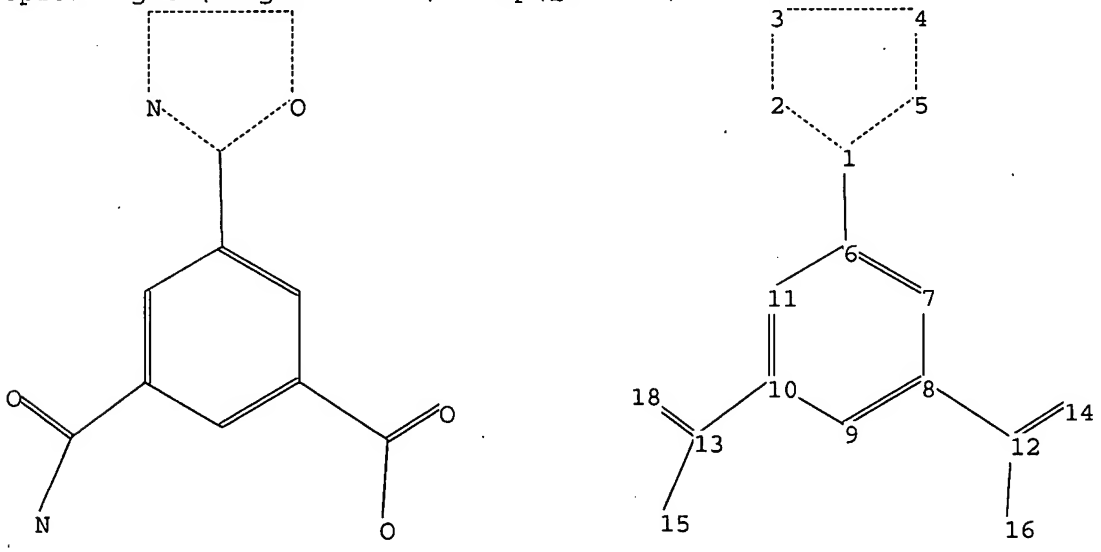
Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10600100.str



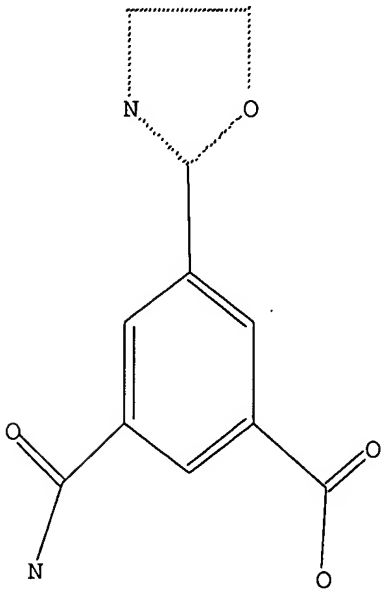
chain nodes :
12 13 14 15 16 18
ring nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
1-6 8-12 10-13 12-14 12-16 13-15 13-18

ring bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 2-3 3-4 4-5 12-14 12-16 13-15 13-18
exact bonds :
1-6 8-12 10-13
normalized bonds :
6-7 6-11 7-8 8-9 9-10 10-11
isolated ring systems :
containing 1 : 6 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 18:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 86 TO ITERATE

100.0% PROCESSED 86 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

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                    BATCH   **COMPLETE**
PROJECTED ITERATIONS:          1164 TO     2276
PROJECTED ANSWERS:                1 TO       80

L2             1 SEA SSS SAM L1

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FULL SEARCH INITIATED 09:25:47 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      1552 TO ITERATE

100.0% PROCESSED     1552 ITERATIONS                                 26 ANSWERS
SEARCH TIME: 00.00.01

L3            26 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     161.33     161.54

FILE 'CAPLUS' ENTERED AT 09:25:52 ON 18 SEP 2005
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FILE COVERS 1907 - 18 Sep 2005  VOL 143 ISS 13
FILE LAST UPDATED: 16 Sep 2005  (20050916/ED)

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  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s l3
L4             4 L3

=> d ibib abs hitstr tot
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L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

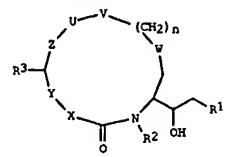
ACCESSION NUMBER: 2005:472134 CAPLUS
DOCUMENT NUMBER: 143:26648
TITLE: Preparation of macrocyclic lactams for treatment of neurological or vascular disorders related to β-amyloid generation and/or aggregation
INVENTOR(S): Auberson, Yves; Betschart, Claudia; Glatthar, Ralf; Laumen, Kurt; Machauer, Rainer; Tintelnot-Blomley, Marina; Troxler, Thomas J.; Veenstra, Siem Jacob
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005049585	A1	20050602	WO 2004-EP12497	20041104

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-25830 A 20031105
OTHER SOURCE(S): MARPAT 143:26648
GI

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



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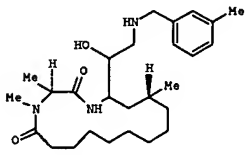


II

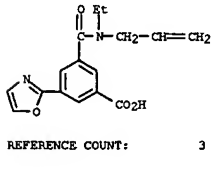
AB The present invention relates to novel macrocyclic compds. of the formula (I) [R1 = each N-(un)substituted CH(Re)C(O)NH2 or (CH2)kNH2 (wherein k = 0-2); R2 = H, C1-4 alkyl; R3 = H, C1-6 alkyl, (un)substituted C1-6 alkyl-OC(O)NH, C3-7 cycloalkyl-OC(O)NH, C3-7 cycloalkyl-C1-4 alkyl-OC(O)NH, aryl-C1-4 alkyl-OC(O)NH, heteroaryl-C1-4 alkyl-OC(O)NH, C1-4 alkyl-C(O)NH, C3-7-cycloalkylC(O)NH, aryl-C(O)NH, aryl-C1-4 alkyl-C(O)NH, heteroaryl-C(O)NH, heteroaryl-C1-4 alkyl-C(O)NH; U = a bond, CF2, CF2CF2, CHF, CHFCHF, cycloprop-1,2-ylene, C1-3 alkylenoxy, C1-8 alkylene, each (un)substituted NH or an aromatic or heteroarom. ring whereby Z and V are in ortho- or meta-position to each other; V = CH:CH, cycloprop-1,2-ylene, CH2CH(OH), CH(OH)CH2, CRhRhCRhRh (wherein Rh = independently H, F, (C:)alkyl); W = C1-6 alkylene, O, S, S(O)2, C(O), C(O)O, OC(O), each (un)substituted NHC(O), C(O)NH, or NH whereby Y and (un)substituted C(O)NH are in meta-position to each other; Y = a bond, O, S(O)2, each (un)substituted S(O)2NH, NHS(O)2, NH, CHOH, C(O)NH, NHC(O), C(O)NHO, or ONHC(O); Z = O, CH2, OF2, CHF, cycloprop-1,2-ylene, a bond; n = 0-5, the number of ring atoms included in the macrocyclic ring being 14, 15, 16 or 17, in free base form or in acid addition salt form]. These compds. are useful as pharmaceuticals for the treatment of neurol. or vascular disorders related to β-amyloid generation and/or aggregation which may include neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis. They inhibit BACE2 (beta-site APP-cleaving enzyme 2) (β-Secretase 2) or cathepsin D, close homologues of the pepsin-type aspartyl proteases and of β-secretase and can be used for the treatment of disorders involving processing by such enzymes. Particularly they inhibit β-secretase and as such inhibit the generation of β-amyloid and the subsequent

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

aggregation into oligomers and fibrils. Thus ring-closing metathesis of hept-6-enoic acid N-[(S)-1-[[(R)-1-(2-chloro-1-hydroxyethyl)-3-methylhept-6-enyl]carbamoyl]ethyl]-N-methylamide in the presence of [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium (Grubbs II catalyst) in CH2Cl2 under refluxing gave (E)-(3S,14R)-16-(2-Chloro-1-hydroxyethyl)-3,4,14-trimethyl-1,4-diazacyclohexadec-10-ene-2,5-dione which was hydrogenated over 10% Pd-C in ethanol to give (3S,14R)-16-(2-Chloro-1-hydroxyethyl)-3,4,14-trimethyl-1,4-diazacyclohexadecane-2,5-dione (II). Cyclization of II by treatment with a mixt. of aq. 1 M NaOH and THF at 0° for 2 h gave (3S,14R)-3,4,14-Trimethyl-16-(oxiran-2-yl)-1,4-diazacyclohexadecane-2,5-dione which underwent amination with 3-methylbenzylamine at 65° for 2 h to give (3S,14R)-16-[1-Hydroxy-2-(3-methylbenzylamino)ethyl]-3,4,14-trimethyl-1,4-diazacyclohexadecane-2,5-dione. The compds. II showed inhibitory activity of <20 μM in at least one of assays on human BACE, BACE-2, cathepsin D, and cellular release of amyloid peptide 1-40.

IT 852878-66-1P, N-Allyl-N-ethyl-5-(oxazol-2-yl)isophthalamic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of macrocyclic lactams for treatment of neurol.
or vascular disorders related to β-amyloid generation and/or aggregation)

RN 852878-66-1 CAPLUS
CN Benzoic acid, 3-[(ethyl-2-propenylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:220301 CAPLUS
DOCUMENT NUMBER: 140:270550
TITLE: A preparation of 1,3-diamino-2-hydroxypropane derivatives as beta-secretase enzyme inhibitors
INVENTOR(S): Fobian, Yvette M.; Freskos, John N.; Jagodzinska, Barbara
PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; Pharmacia & Upjohn
SOURCE: PCT Int. Appl., 535 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022523	A2	20040318	WO 2003-US28116	20030908
WO 2004022523	A3	20040910		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2497979	AA	20040318	CA 2003-2497979	20030908
US 2004214890	A1	20041028	US 2003-657567	20030908
EP 1534693	A2	20050601	EP 2003-749520	20030908

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

BR 2003014071	A	20050705	BR 2003-14071	20030908

PRIORITY APPLN. INFO.: US 2002-408783P P 20020906
WO 2003-US28116 W 20030908

OTHER SOURCE(S): MARPAT 140:270550
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to diamino(hydroxy)propane derivs. of formula I [wherein: R1 = -(CH2)1-2-S(O)0-2-(C1-6 alkyl) or (un)substituted (cyclo)alkyl, alk(en/yn)yl, (hetero)aryl, etc.; R2 = H, C1-6 alkyl optionally substituted with 1-3 substituents, (CH2)0-4-(hetero)aryl, C2-6 alk(en/yn)yl, etc.; R3 = H, C1-6 alkyl optionally substituted with 1-3 substituents, (CH2)0-4-(hetero)aryl, etc.; R4 = C1-10 alkyl optionally substituted with 1-3 substituents, -(CH2)0-3-cycloalkyl, -(CR7R8)0-4-(hetero)aryl, etc.; one of R5 and R6 is H and the other is -C(O)(CR9R10)1-6-X-R11, etc.; R7 and R8 are independently selected from H, alkyl, hydroxyalkyl, alk(en/yn)yl, etc.; R9 and R10 are independently selected from H or C1-10 alkyl; R11 = (hetero)aryl, optionally substituted C1-10 alkyl, or C3-8 cycloalkyl, etc.; X = O, S, SO2, etc.]. Compds. I include inhibitors of beta-secretase enzyme useful in the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta-peptide in a mammal. Biol. examples include beta-secretase

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

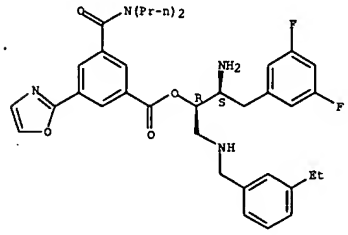
inhibition, assays using synthetic oligopeptide-substrates, inhibition of A beta prodn. in human patients, etc. For instance, compd. II (prepn. 8) was prepd. via amidation of benzoic acid deriv. III by diamino(hydroxy)propane deriv. IV and subsequent Boc-cleavage (no yield data). Using 19F-NMR an intramol. acyl-migration was obsd. when compd. II was dissolved in DMSO-d6 and pH 4 buffer soln. was added.

IT **674311-20-7P 674311-21-8P 674311-24-1P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; preparation of diamino(hydroxy)propane derivs. useful as beta-secretase inhibitors)

RN 674311-20-7 CAPLUS

CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[(3-ethylphenyl)methyl]amino]methyl]propyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



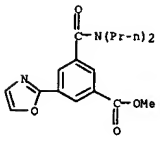
●2 HCl

RN 674311-21-8 CAPLUS

CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[1-(3-ethylphenyl)cyclopropyl]amino]methyl]propyl ester, dihydrochloride (9CI) (CA INDEX NAME)

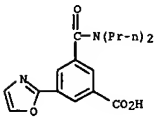
Absolute stereochemistry.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 597563-26-3 CAPLUS

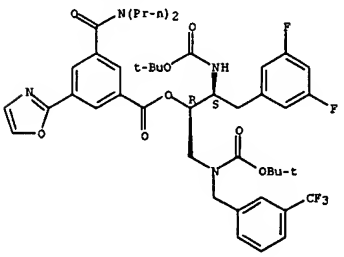
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)



RN 674311-07-0 CAPLUS

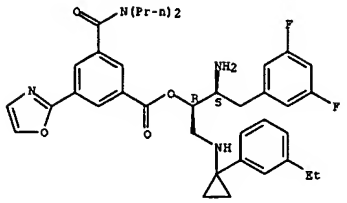
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-3-(3,5-difluorophenyl)-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-[[[(1,1-dimethylethoxy)carbonyl][[3-(trifluoromethyl)phenyl]methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **674311-05-8P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

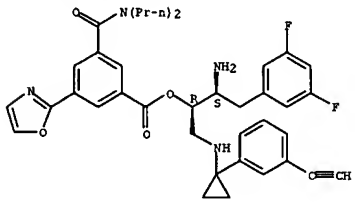


●2 HCl

RN 674311-24-1 CAPLUS

CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[1-(3-ethynylphenyl)cyclopropyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **597561-63-2P 597563-26-3P 674311-07-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of diamino(hydroxy)propane derivs. useful as beta-secretase inhibitors)

RN 597561-63-2 CAPLUS

CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, methyl ester (9CI) (CA INDEX NAME)

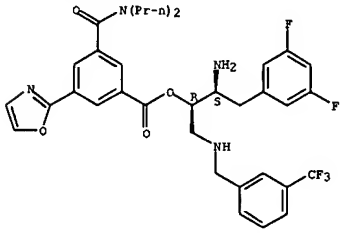
L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

(Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of diamino(hydroxy)propane derivs. useful as beta-secretase inhibitors)

RN 674311-05-8 CAPLUS

CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[[3-(trifluoromethyl)phenyl]methyl]amino]methyl]propyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

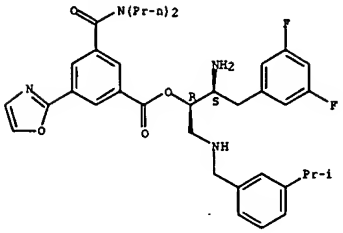
IT **674311-29-6P 674311-31-0P 674311-32-1P**
674311-51-4P 674311-55-8P 674311-60-5P
674311-61-6P 674311-64-9P 674311-72-9P
674311-92-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diamino(hydroxy)propane derivs. useful as beta-secretase inhibitors)

RN 674311-29-6 CAPLUS

CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[[3-(1-methylethyl)phenyl]methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

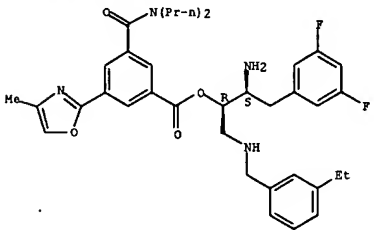
Absolute stereochemistry.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 674311-31-0 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(4-methyl-2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[(3-ethylphenyl)methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

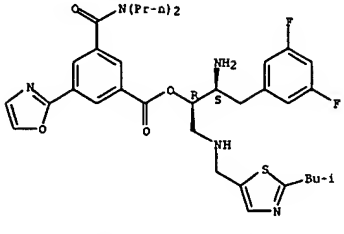
Absolute stereochemistry.



RN 674311-32-1 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[[2-(2-methylpropyl)-5-thiazolyl]methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

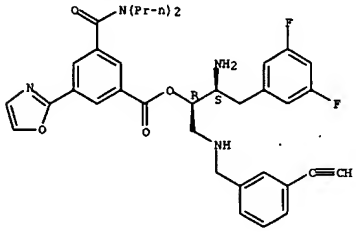
Absolute stereochemistry.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 674311-51-4 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[(3-ethynylphenyl)methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

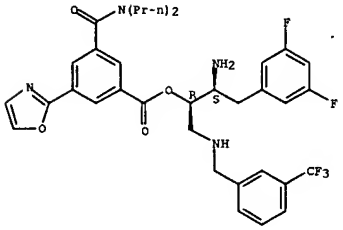
Absolute stereochemistry.



RN 674311-55-8 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[(3-(trifluoromethyl)phenyl]methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

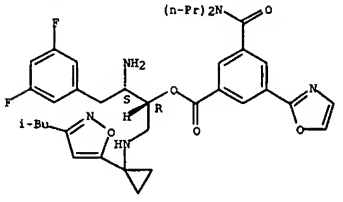
Absolute stereochemistry.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 674311-60-5 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[1-(3-(2-methylpropyl)-5-isoxazolyl]cyclopropyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

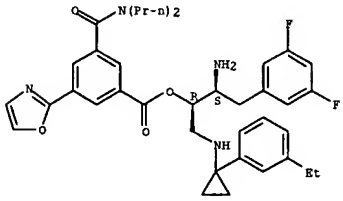
Absolute stereochemistry.



RN 674311-61-6 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[1-(3-ethylphenyl)cyclopropyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

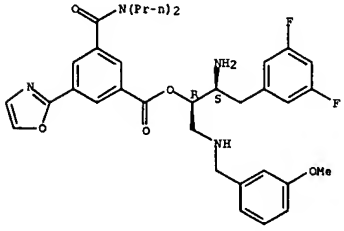
Absolute stereochemistry.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 674311-64-9 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[(3-methoxyphenyl)methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

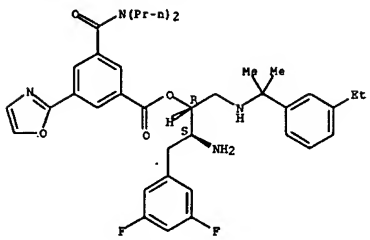
Absolute stereochemistry.



RN 674311-72-9 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[1-(3-ethylphenyl)-1-methylethyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

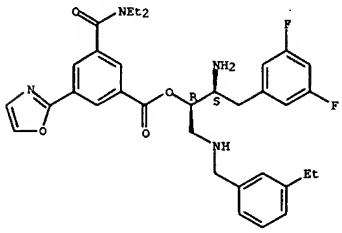
Absolute stereochemistry.

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 674311-92-3 CAPLUS
CN Benzoic acid, 3-[(diethylamino)carbonyl]-5-(2-oxazolyl)-, (1R,2S)-2-amino-3-(3,5-difluorophenyl)-1-[[[(3-ethylphenyl)methyl]amino]methyl]propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:2867 CAPLUS
DOCUMENT NUMBER: 140:59634
TITLE: Process for preparing 5-(1,3-oxazol-2-yl)benzoic acid derivatives
INVENTOR(S): Reeder, Michael R.; Imbordino, Rick J.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000821	A1	20031231	WO 2003-US19585	20030620
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2489988	AA	20031231	CA 2003-2489988	20030620
US 20040063965	A1	20040401	US 2003-600100	20030620
BR 2003012439	A	20050510	BR 2003-12439	20030620
EP 1532123	A1	20050525	EP 2003-761206	20030620
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.:
US 2002-390285P P 20020620
US 2003-450478P P 20030227
WO 2003-US19585 W 20030620

OTHER SOURCE(S): CASREACT 140:59634; MARPAT 140:59634
GI

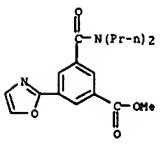
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed are compds. of formula (I) [R1 = C1-6 alkoxy, OH; R2, R3 = H, Ph, C1-4 alkyl; or R2 and R3 and the carbons to which they are attached form a benzo ring, which is optionally substituted with C1-4 alkyl, C1-4 alkoxy, or dialkylamino; R6 = C1-6 alkoxy or NR4R5; R4, R5 = C1-6 alkyl] and a process to prepare the compound I, by coupling a zinc chloride/optionally substituted oxazole adduct (II) (R2, R3 = same as above) and an compound of formula (III) (X = Br, iodo, OSO2CF3, OSO2Me) in the presence of a transition metal catalyst. The compds. I are used to prepare compds. of formula (IV) [R2, R3, R6 = same as above; R10 = R10 = -(CH2)1-2-S(O)0-2-(C1-6 alkyl), or each (un)substituted C1-10 alkyl, C2-6 alkenyl, or C2-6 alkynyl, aryl, heteroaryl, heterocyclyl, C1-6-alkylaryl, C1-6 alkylheteroaryl, or C1-6 alkylheterocyclyl, where the ring portions

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
of each are optionally substituted; R20, R30 = H, each (un)substituted C1-6 alkyl, CONH2, or SO2NH2, (CH2)0-4-aryl, (CH2)0-4-heteroaryl, C2-6 alkenyl, C2-6 alkynyl, CO2H, CO2-(C1-4 alkyl); or R20, R30 and the carbon to which they are attached form a C3-7 carbocycle, wherein one carbon atom is optionally replaced by a group selected from O, S, SO2, or (un)substituted NH; Rc = H, (CR245R250)0-4-aryl, (CR245R250)0-4-heteroaryl, (CR245R250)0-4-heterocyclyl, (CR245R250)0-4-arylheteroaryl, (CR245R250)0-4-arylheterocyclyl, (CR245R250)0-4-arylaryl, (CR245R250)0-4-heteroarylaryl, (CR245R250)0-4-heteroarylheterocyclyl, (CR245R250)0-4-heteroarylheteroaryl, etc.; R245, R250 = H, C1-4 alkyl, C1-4 alkylaryl, C1-4 alkylheteroaryl, C1-4 hydroxyalkyl, C1-4 alkoxy, C1-4 haloalkoxy, (CH2)0-4-C3-7 cycloalkyl, Ph, etc.; or R245 and R250 are taken together with the carbon to which they are attached to form a C3-7 carbocycle, where one carbon atom is optionally replaced by a heteroatom selected from O, S, SO2, and (un)substituted NH] in the treatment of Alzheimer's disease and related conditions. Thus, BuLi (1.4 equiv) was added dropwise over 30 min to a stirred, cooled (-78°) mixt. of 1,3-oxazole (1.3 equiv) in THF, while maintaining the mixt. at a temp. bellow about -55°, stirred for 30 min, treated with solid ZnCl2 (3 equiv) in 3-10 portions over about 10-15 min, allowed to warm to 20-25°, and stirred for an addnl. 10 min to give a soln. of 2-oxazolylzinc chloride. The latter zinc chloride adduct was added over a period of 2 h to a mixt. of Me 3-bromo-5-[(dipropylamino)carbonyl]benzoate (V) and tetrakis(triphenylphosphine) palladium (5 mol%) in THF at 50°, and stirred at 50° until no V was obsd. by HPLC (usually about 1 h) to give, after workup and silica gel chromatog., Me 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (VI). VI was sapond. by NaOH in aq. MeOH and acidified with concd. HCl to give 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid which was treated with CDI in THF at room temp. for 1 h, added slowly over to a cooled (-35°) mixt. of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol in THF, warmed to 0°, and stirred until the completion of the reaction was obsd. by HPLC to give, after workup and silica gel chromatog., N1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N3,N3-dipropylisophthalamide (VII).

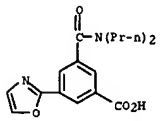
IT 597561-63-2P, Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate 597563-26-3P, 3-[(Dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing oxazolylbenzoic acid derivs. as intermediates for anti-Alzheimer's agent)

RN 597561-63-2 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, methyl ester (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

RN 597563-26-3 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:412801 CAPLUS
DOCUMENT NUMBER: 139:245782
TITLE: Preparation of N,N'-substituted-1,3-diamino-2-hydroxypropanes for treating Alzheimer's disease
INVENTOR(S): Varghese, John; Maillard, Michel; Jagodzinska, Barbara; Beck, James P.; Gailunas, Andrea; Fang, Larry; Sealy, Jennifer; Tenbrink, Ruth; Freskos, John; Mickelson, John; Samala, Lakshman; Hom, Roy
PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; Pharmacia & Upjohn Company
SOURCE: PCT Int. Appl., 1243 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040096	A2	20030515	WO 2002-XA36072	20021108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003040096	A2	20030515	WO 2002-US36072	20021108
WO 2003040096	A3	20040506		
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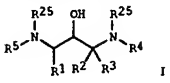
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-337122P P 20011108
US 2001-344086P P 20011228
US 2002-345635P P 20020103
WO 2002-US36072 A 20021108

OTHER SOURCE(S): MARPAT 139:245782
GI

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



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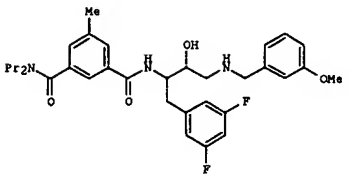


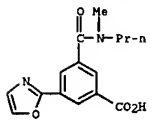
II

AB The title compds. [I; R1 = (un)substituted alkyl, alkenyl, alkynyl, etc.; R2 = H, alkyl, haloalkyl, alkenyl, etc.; R3 = H, alkyl, haloalkyl, alkenyl, etc.; or R2 and R3 are taken together with the carbon to which they are attached to form a carbocycle of 3-7 carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of O, S, SO2, (un)substituted NH; R4 = alkyl, haloalkyl, hydroxyalkyl, etc.; R5 = R6X (wherein X = CO, SO2, (un)substituted CH2; R6 = (un)substituted Ph, naphthyl, indanyl, etc.); R25 = H, alkyl, alkoxy, etc.] which have activity as inhibitors of β-secretase and are therefore useful in treating a variety of disorders such as Alzheimer's disease, were prepared E.g., a multi-step synthesis of (1S,2R)-II, starting from (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid, was given. The compds. I showed IC50 of < 20 μM in cell free inhibition assay utilizing a synthetic APP substrate. This is a Part 2 of 1-2 series.

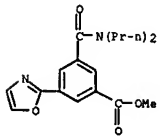
IT **597561-61-0P 597561-63-2P 597563-21-8P**
597563-22-9P 597563-26-3P 597563-28-5P
597563-29-6P 597563-31-0P 597563-32-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N,N'-substituted-1,3-diamino-2-hydroxypropanes for treating
Alzheimer's disease)

RN 597561-61-0 CAPLUS
CN Benzoic acid, 3-[(methylpropylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)

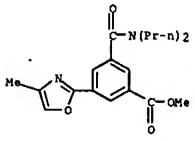
L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



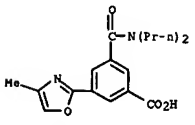
RN 597561-63-2 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)-, methyl ester (9CI) (CA INDEX NAME)



RN 597563-21-8 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(4-methyl-2-oxazolyl)-, methyl ester (9CI) (CA INDEX NAME)

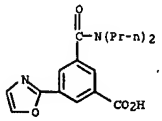


RN 597563-22-9 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(4-methyl-2-oxazolyl)- (9CI) (CA INDEX NAME)

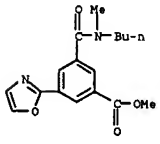


L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

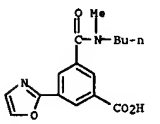
RN 597563-26-3 CAPLUS
CN Benzoic acid, 3-[(dipropylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)



RN 597563-28-5 CAPLUS
CN Benzoic acid, 3-[(butylmethylamino)carbonyl]-5-(2-oxazolyl)-, methyl ester (9CI) (CA INDEX NAME)

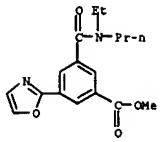


RN 597563-29-6 CAPLUS
CN Benzoic acid, 3-[(butylmethylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)



RN 597563-31-0 CAPLUS
CN Benzoic acid, 3-[(ethylpropylamino)carbonyl]-5-(2-oxazolyl)-, methyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 597563-32-1 CAPLUS
CN Benzoic acid, 3-[(ethylpropylamino)carbonyl]-5-(2-oxazolyl)- (9CI) (CA INDEX NAME)